Analysis of Acupoint Selection and Combinations in Acupuncture Treatment of Asthma Based on Data Mining

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Research

Abstract

Background: Asthma is a highly prevalent respiratory disease that remains difficult to control. Acupuncture, as an important alternative therapeutic modality in preventing and treating asthma, is widely used in the world due to its promising efficacy and safety. Although acupoint selection and combinations are critical to therapeutic effects of acupuncture, its fundamental rules for asthma have not been fully understood. Thus, using data mining, the present study aimed to discover the most effective acupoints and combinations in the acupuncture treatment of asthma..

Methods: Controlled clinical trials (CCTs) of acupuncture treatment for asthma were searched and retrieved from databases including Chinese National Knowledge Infrastructure (CNKI), Wanfang, and PubMed. Data regarding the main acupoints prescribed in these clinical trials was collected and quantified. A network analysis was performed to uncover the interconnections between the acupoints. Additionally, hierarchical clustering analysis and association rule mining were conducted to discover the potential acupoint combinations.

Results: A total of 183 CCTs were retrieved. *Feishu* (BL13), *Dingchuan* (EX-B1), *Dazhui* (GV14), *Shengshu* (BL23), *Pishu* (BL20), and *Fengmen* (BL12) appeared to be the most frequently used acupoints for asthma. While the Bladder Meridian of Foot *Taiyang*, the Governor Vessel, and the Conception Vessel, compared to other meridians, were found to be the more commonly selected meridians. In the acupoint interconnection network, *Feishu* (BL13), *Fengmen* (BL12), *Dingchuan* (EX-B1), and *Dazhui* (GV14) were defined as key node acupoints. Moreover, acupoint clustering analysis revealed the treatment principle of "facilitating the flow of the lung Qi, tonifying spleen and kidney, and treating both the symptoms and root causes". Association rule mining analysis demonstrated that the combination of *Pishu*, *Shenshu*, *Feishu*, and *Dingchuan*, as well as that of *Feishu*, *Dazhui*, and *Fengmen* were potential acupoint combinations that should be selected with priority in asthma treatment.

Conclusion: Based on a data mining analysis of published CCTs, this study provides valuable information regarding the selection of the most effective acupoints and combinations for clinical acupuncture practice and experimental study aimed at the prevention and treatment of asthma.

Background

Asthma is a common chronic respiratory disease characterized by inflammation of the airways and recurrent airflow obstruction, affecting more than 300 million people worldwide and causing approximately 400,000 deaths worldwide annually [1]. In traditional Chinese medicine (TCM), asthma is attributed to the categories of *Xiao* and *Chuan*, which mean "wheezing" and "dyspnea" (breathlessness), respectively. Asthma tends to be a lifelong condition, impairing an individual's quality of life, and is often associated with high health care expenditures, including both direct and indirect costs [2]. To date, the most popular option for the management of asthma currently available is the combination of inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABAs). Although the use of these drugs helps to

reduce the frequency and severity of asthma exacerbations in the short term, their long-term use has been linked to drug resistance as well as a number of adverse side effects, including growth retardation in children, osteoporosis, oral candidiasis infection, and muscle tremors [3, 4]. Moreover, it is thought that approximately 5–10% of patients with severe refractory asthma respond poorly or not at all to the currently available drug therapies [5]. Therefore, there is still a great clinical need to discover new asthma therapeutic methods that are more effective, safe, and economical for improving the disease state, symptoms, and quality of life in asthma patients [6].

In China and other Asian countries, acupuncture is an important alternative therapeutic modality in preventing and treating various diseases and health problems due to its promising efficacy and safety. Ancient Chinese doctors believed that the human body's vital energy (*Jing-Qi* in Chinese) and blood circulates along a pathway system composed of meridians and collaterals (*Jing-Luo* in Chinese) to nourish and connect the solid-hollow viscera. The meridian *Qi* can flow and converge onto specific loci of the human body, which are called "acupuncture points" or "acupoints". In acupuncture treatment, sharp, thin needles are inserted into specific acupoints to assist the body in regulating the flow of meridian *Qi* and achieving balance and harmony. Records regarding the acupuncture treatment of asthma can be traced back to the *Yellow Emperor's Inner Canon* (*Huangdi Neijing* in Chinese), the earliest existing works on the theories and practices of TCM, which stated "*If a patient has rebellious Qi with rapid, hoarse breathing, acupuncture Tiantu (CV22) point. If the rebellious Qi rushing upwards to the throat, acupuncture Daying (ST5) point*". Acupuncture has more than 2,000-year history of in China as a non-pharmacological therapy for asthma with rich accumulated clinical evidence. Over the last few decades, the practice of acupuncture as an asthma treatment has been widely used due to its remarkable therapeutic effect and limited adverse effects in many of the countries throughout the world. The World Health Organization (WHO) endorsed acupuncture for asthma and 42 other indications in 1979 [7], and the National Institutes of Health (NIH) issued a consensus statement in 1997 proposing acupuncture as an effective treatment option in comprehensive management programs for several health problems, including asthma [8]. Previous studies by ourselves and others have showed that acupuncture treatment can reduce the frequency and severity of asthma exacerbations, improve lung function, inhibit the airway inflammatory response dominated by type 2 T helper cells, and decrease medication dosages for patients with asthma [9–13]. Moreover, a recent meta-analysis demonstrated that conventional treatments plus acupuncture significantly improved symptom response rates clinically and statistically when compared with conventional treatments alone, suggesting that acupuncture is a promising treatment for asthma [14].

Acupoint selection and combinations are considered to be the core of the acupuncture treatment system. In clinical practice, acupuncturists often combine two or more acupoints to enhance the synergy between acupoints and improve the therapeutic effect of acupuncture. The increasing number of successful acupuncture practices for asthma have used a large number of acupoint prescriptions, in which the compatibility of meridians and acupoints exhibits great complexity, contradictoriness, and uncertainty directly linked to the clinical efficacy of acupuncture treatment. Therefore, it is necessary to use existing data to analyse the principles of acupoint selection and combination and construct superior acupoint

combination programs for different TCM syndromes of asthma in order develop the therapeutic potential of acupuncture. Data mining techniques that apply algorithms, such as classification, clustering, and association rules, are powerful statistical exploratory data analysis tools that have been widely employed to uncover hidden concepts and relations within big datasets. Studies based on data mining approaches have increased knowledge regarding the selection and combination of acupoints and provided some valuable suggestions for acupuncture treatment in, for example, chronic obstructive pulmonary disease [15], Alzheimer's disease [16], dry eye disease [17], and among others. In this study, we intended to investigate the principles of acupoint selection and combination using data mining techniques based on acupoint data from the literature on acupuncture treatment for asthma in the past 20 years with the purpose of informing the selection of the most effective acupoints and combinations in clinical acupuncture practice and experimental study for the prevention and treatment of asthma.

Materials And Methods

Literature source and search strategy

The electronic literature databases PubMed (https://pubmed.ncbi.nlm.nih.gov),Chinese National Knowledge Infrastructure (CNKI, https://www.cnki.net), and Wanfang (http://www.wanfangdata.com.cn) were searched for research on acupuncture treatments for asthma published between January 2010 and December 2019, with the language restricted to English and Chinese. The search strategy combined the search terms: (i) "acupuncture" or "electroacupuncture" or "moxibustion" or "acupoint" or "meridian" or "cupping", and (ii) "asthma". When searching the Chinese database, the Chinese medical subject terms were consistent with their Chinese translations used in medical subject headings, and the TCM subject terms were related to acupuncture and asthma, such as "medicinal vesiculation" (*Tianjiu* in Chinese) and "gasping syndrome" (*Chuanzheng* in Chinese), which were also searched.

Literature screening

Duplicate and irrelevant articles were removed after reading the titles and abstracts. The other retrieved articles were further screened according to the following inclusion criteria and exclusion criteria (Fig. 1).

The inclusion criteria included: (i) controlled clinical trials (CCTs) with acupuncture as the primary therapeutic method; (ii) the patient was diagnosed with asthma according to the diagnostic criteria for asthma disease; and (iii) acupuncture therapies were defined as follows: manual acupuncture or electroacupuncture at acupoints, moxibustion, simultaneous intervention of acupuncture and moxibustion, cupping, acupoint injection, acupoint catgut embedding, and the combination of two or more of the above therapies; (iv) the latest article would be included in case of duplicate publications. In terms of exclusion criteria, the following papers were excluded: reviews, systematic reviews or meta-analyses, animal experiments, case reports, trials only stimulating *Ashi* acupoints or non-acupoint trigger points based on anatomy and physiology, and some special acupuncture therapies selecting acupoints and meridians according to the time of day and solar terms.

Data extraction

Information data from all the eligible papers, including the study design, sample size, age and gender of the participants, main acupoints selected, meridians, frequencies of acupoints, specific acupoints, therapy methods, and outcome measures, were extracted by one reviewer to establish a dataset of acupuncture treatment for asthma, while another reviewer checked for the accuracy and completeness of the input information. All descriptions of acupoints and meridians in the included prescriptions were unified and standardized according to the WHO Standard Acupuncture Point Locations in the Western Pacific Region and China National Standard "Naming and Positioning of Acupoints" (GB/T 12346 – 2006).

Quality assessment

In using Cochrane Collaboration's tool for assessing the risk of bias, the quality of the included controlled clinical trials was assessed based on the following seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Acupoint interconnection network analysis

The interconnection network of acupoints in all the included prescriptions was analyzed and visually constructed using Cytoscape software (version 3.7.2). Acupoints (defined as the "nodes" of the network) appearing together in a prescription would be connected by "edges" in the network. The more frequently used acupoints have thicker edges on their connections. The centrality of the acupoints in the correlation network was evaluated using graph theory. The degree centrality is measured by the total amount of direct connections with the other nodes; betweenness centrality measures the extent to which a node lies on the shortest path between other nodes and is used to evaluate the "mediation" role of the node in a network; and the closeness centrality of a node measures its average distance to all other nodes [18].

Hierarchical clustering analysis

A hierarchical clustering analysis of the acupoints for asthma treatment was carried out by running the "cluster" package with R software (version 4.0.2). The acupoints in a prescription were first converted into dichotomous variables, with "1" indicating the occurrence of an acupoint and "0" indicating the absence, and the squared Euclidean distance (SED) was used as the measure of the distance between acupoints. The Ward's minimum variance method was employed for clustering to minimize the total variance within the cluster.

Association rule analysis

Association rule analysis refers to the process of determining patterns that occur frequently within a given transaction base, such as identifying frequent itemsets and frequent itemset combinations [19]. An association rule is an implication expression of the form X→Y, where the light-hand side (LHS, X) is called the "antecedent" or the "premise" and the right-hand side (RHS, Y) is the "consequent" or the "conclusion".

The strength of a rule X→Y is evaluated by three important metrics: "support", "confidence", and "lift". The support of X→Y refers to the frequency that itemset X and itemset Y appear together in the transaction base. The confidence of X→Y indicates the conditional probability that the itemset Y appears in the presence of itemset X. The lift of X→Y is the fraction of the observed support of X→Y to that of expected if X and Y were independent and indicates the degree to which two itemsets are dependent on one another, which makes the rule valuable. Generally, the lift should be bigger than one for a rule to be interesting [20]. Apriori is a widely used algorithm using a layer-by-layer iterative search technique to mine relationships between itemsets and generate association rules. In this study, the R language was used for running the Apriori algorithm with the existing "*arules*" and "*arulesViz*" packages in order to find strong association rules between acupoints or meridians based on "lift" values.

Results

Summary of included studies

Database searching identified 1,073 records in CNKI and Wanfang and 336 records in PubMed. After the removal of duplicates and irrelevant articles by title and abstract reading, a total of 1,320 papers were included for further screening, of which 183 eligible papers were retrieved according to the inclusion and exclusion criteria and thus subjected to our analysis (Fig. 1). The quality assessment in terms of the overall bias of these 183 CCTs is presented in Fig. 2. The proportion of CCTs with an unclear risk of bias was 86% and 98% for all CCTs due to allocation concealment, and blinding of outcome data, respectively. A total of 177 (96.7%) CCTs did not state any details regarding the blinding of participants and personnel to the intervention assignment and were judged as having a high risk of bias. The most likely reason for this is that fully double-blinding is difficult for non-pharmacological treatments like acupuncture, and most types of placebo acupuncture fail to profoundly blind acupuncturists.

Frequencies of acupoints and meridians in asthma treatment

Among the 183 qualified studies, a total of acupoint frequency of 1,030 times, which corresponded to 75 unique acupoints, were found to be used for the treatment of asthma. The top 10 most frequently used acupoints were found to be *Feishu* (BL13, 89%), *Dingchuan* (EX-B1, 58%), *Dazhui* (GV14, 41%), *Shenshu* (BL23, 36%), *Pishu* (BL20, 31%), *Fengmen* (BL12, 30%), *Zusanli* (ST36, 29%), *Danzhong* (CV17, 25%), *Gaohuang* (BL43, 19%), and *Tiantu* (CV22, 18%) (Fig. 3a). All of the 75 applied unique acupoints are distributed across 12 meridians, covering 10 regular meridians, as well as the Conception Vessel, and Governor Vessel. The most frequently used meridian was found to be the Bladder Meridian of Foot *Taiyang* (92%) followed by the Governor Vessel (42%) and Conception Vessel (38%) (Fig. 3b). However, no acupoint belonged to the Large Intestine Meridian of Hand *Yangming*, and the Heart Meridian of Hand *Shaoyin* was selected in the retrieved CCTs. Although extraordinary acupoints (58%) were also found to be frequently used, their distribution has not been analyzed here because they do not belong to any

meridians. Notably, *Yang* meridians were used more frequently (68%) compared to the *Yin* meridians (32%).

Interconnection network analysis of acupoints for asthma treatment

In order to explore the acupoint–acupoint interconnections among the 183 acupoint prescriptions for asthma, Cytoscape software was used to visually construct an acupoint interconnection network consisting of 75 nodes and 808 edges (Fig. 4). "Node" is used to represent the unique acupoint, and "Edge" is used to represent the cooccurrence of two acupoints in a prescription. The centrality of the key acupoints in the network, evaluated based on degree centrality, betweenness centrality, and closeness centrality is shown in Table 1. It can be seen that *Feishu* (BL13), *Dingchuan* (EX-B1), *Fengmen* (BL12), *Dazhui* (GV14), *Danzhong* (CV17), *Shenshu* (BL23), *Zusanli* (ST36), *Lieque* (LU7), and *Pishu* (BL20) are the core acupoints of this whole complex network based on degree centrality.

Table 1
The centrality of acupoints in the acupoint interconnection network

Acupoint	Meridian Distribution	Degree Centrality	Closeness Centrality	Betweenness Centrality
BL13	BL	68	0.90243902	0.16490468
BL12	BL	52	0.75510204	0.03646454
EX-B1	EX	52	0.7628866	0.04933657
GV14	GV	51	0.7628866	0.04715317
CV17	CV	51	0.7628866	0.04324215
BL23	BL	49	0.74747475	0.03619628
ST36	ST	47	0.73267327	0.05363298
LU7	LU	43	0.69811321	0.0233019
BL20	BL	42	0.69811321	0.02433983
BL15	BL	40	0.68518519	0.01335119
ST40	ST	39	0.67889908	0.02597771
LU5	LU	39	0.67889908	0.01561269
LU1	LU	38	0.66666667	0.01741898
PC6	PC	38	0.66666667	0.04266471
LI4	LI	37	0.66666667	0.03203523
BL43	BL	36	0.65486726	0.03534629
LU9	LU	35	0.65486726	0.01920652
LU6	LU	34	0.64912281	0.01336027
CV4	CV	34	0.64912281	0.00643126
LU10	LU	33	0.63793103	0.01187024

Hierarchical clustering analysis of acupoints for asthma treatment

Hierarchical clustering is a set of statistical analysis techniques that categorize research objects into optimally homogeneous groups based on measures of similarity. Using Ward's minimum variance method, acupoints with a frequency greater than 2 were clustered into five major clusters: Cluster 1 include *Feishu* (BL13) and *Dingchuan* (EX-B1); Cluster 2 include *Lieque* (LU7) and *Yuji* (LU10); Cluster 3 include *Dazhui* (GV14) and *Fengmen* (BL12); Cluster 4 include *Pishu* (BL20) and *Shenshu* (BL23); and

Cluster 5 include *Danzhong* (CV17), *Tiantu* (CV22), *Gaohuang* (BL43), *Zusanli* (ST36), and *Fenglong* (ST40). The other acupoints were clustered into minor subgroups (Fig. 5).

Association rule mining of acupoints for asthma treatment

A total of 60 acupoint association rules were obtained using the Apriori algorithm, in which the minimum support required was set to 15%, the minimum confidence required was set to 30%, and the maximum number of lift-hand-sides was set to 2 (Fig. 6a). Among these association rules, the minimum lift was 0.96, and the maximum lift was 2.69. The detailed information of the support, confidence, and lift of these acupoint association rules are shown Supplementary Table 1. The top 10 most frequently used acupoint combinations, as indicated by the association rule lifts, were found to be {BL20,EX-B1}≥{BL23}, {BL20}≥{BL23}, {BL23}≥{BL20}, {BL13,BL20}≥{BL23}, {BL13,BL23}≥{BL20}, {BL23,EX-B1}≥{BL20}, {BL13,BL43}≥{EX-B1}, {BL13,GV14}≥{BL12}, {BL43}≥{EX-B1}, and {BL12,BL13}≥{GV14} (Fig. 6b). In addition, we also mined the association rules of specific acupoints located on the 14 meridians with special curative effects as well as the association rules of meridians applied in the included prescriptions. The results demonstrated that the most frequently used combination of specific acupoints was {Connecting Point, Five Transport Points}≥{Confluence Points of the Eight Vessels} (Supplementary Table 2, and Supplementary Fig. 1), while the most frequently used combination of meridians was {Bladder Meridian of Foot *Taiyang*, Stomach Meridian of Foot *Yangming*} ≥ {Conception Vessel} (Supplementary Table 3, and Supplementary Fig. 2).

Discussion

The efficacy evaluation of clinical trials of acupuncture is not only related to the randomization and blinding process, control group setting, and main endpoints but also closely associated with the acupuncture treatment procedure, including the selection and combination of acupoints, acupuncture methods, and treatment regimen. In particular, selections and combinations of acupoints according to the theory of meridians and acupoints as well as syndrome differentiation in TCM are of vital importance to the full realization of the therapeutic effects of acupuncture, which is a topic that has not been strictly studied in some randomized controlled clinical trials, leading to negative evaluations of acupuncture for asthma treatment. Thus, using data mining technology to analyze the effective acupoints in acupuncture clinical trials is helpful in improving the selection and combination of acupoints in clinical and experimental studies of acupuncture for asthma treatment.

In the 183 CCTs included in the analysis, a total of 8,746 patients with asthma received acupuncture treatment with an average clinical effective rate of 92 ± 6.71%. In parallel, clinical trials with an effective rate of more than 90% accounted for 83% of the total trials analyzed, indicating the significant therapeutic implications of treatment with acupuncture. *Feishu* (BL13) was the most frequently used acupoint in all of these clinical trials with a total frequency of 162. Also, this acupoint was in the most critical position of the complex acupoint correlation network, with the highest degree centrality (68), betweenness centrality (0.165), and closeness centrality (0.902). *Feishu* is an important acupoint for

treating respiratory diseases, including asthma in TCM. It is the acupoint where the lung meridian *Qi* is infused into the back and is located in the projection area of the lung with the function of regulating lung meridian *Qi*. It has been demonstrated that acupuncture at *Feishu* inhibits acetylcholine synthesis and restores muscarinic acetylcholine receptor M2 expression in the lung of an asthma model [21]. Specifically, moxibustion at *Feishu* was shown to inhibit airway inflammatory responses in an asthmatic animal model [22]. Another of the most frequently used acupoints was found to be *Dingchuan* (EX-B1), with a total frequency of 106. *Dingchuan* is an extraordinary acupoint located on the back, 0.5 *cun* lateral to the side of *Dazhui* (GV14), and is located under the spinous process of the seventh cervical vertebra. Increased skin impedance has been found at the *Dingchuan* point in asthmatic patients when compared with healthy individuals [23]. Notably, *Dazhui*, the crossing point of three *yang* meridians and the Governor Vessel, is the third most frequently used acupoint for asthma, with the function of reinforcing the vital *Qi* to relieve asthmatic symptoms. *Dingchuan* and *Dazhui* are mainly located near the cervical sympathetic nerve trunk and the thoracic 1–4 sympathetic chain, where the sympathetic neurons that innervate the lungs and airways are distributed. Thus, acupuncturists will treat nearby acupoints at the same time as *Dazhui* and *Dingchuan*, like *Dazhu* (BL11) and the extraordinary acupoint, *Chuanxi*. Another key node in the acupoint correlation network is *Fengmen* (BL12), which has high degree centrality and closeness centrality. It is believed in TCM that this acupoint can regulate the flow of meridian *Qi* and can be used to dredge and activate the lung meridian, thereby treating pulmonary diseases.

In addition, the back-shu acupoints, including *Feishu*, *Pishu* (BL20), and *Shenshu* (BL23), are a type of specific acupoints commonly used in the treatment of asthma, accounting for 92% of the total frequency of acupoints. The back-shu acupoints are points on the back where the *Qi* and blood of respective *zang-fu* organs are infused. They are specifically located on either side of the vertebral column, in close proximity to the spinal dorsal root ganglia and within the innervation range of their respective *zang-fu* ganglia or the adjacent ganglion segments not exceeding the distance of more than two spinal ganglion segments. It has been reported that acupuncture at back-shu acupoints has an inhibitory effect on the uptake of neurotrophic factors, and the synthesis and release of substance P in dorsal root ganglia, resulting in the relief of airway neurogenic inflammation in asthma [24]. According to the TCM theory, the pathogenesis of asthma is closely linked to the aberrant functions of the lung, spleen, stomach, liver, kidney, and among other *zang-fu* organs. As mentioned in the *Huangdi Neijing*, "*All the five zang organs and six fu organs make people cough and wheeze, not only the lung*". The Governor Vessel and the Conception Vessel travel along the posterior midline and anterior midline of the human body, respectively, and are closely connected to the above-mentioned *zang-fu* organs. At the same time, the energy *Qi* of these *zang-fu* organs is infused into the corresponding back-shu acupoints distributed on the Bladder Meridian of Foot *Taiyang*. Therefore, as our results show, the Bladder Meridian of Foot *Taiyang*, the Governor Vessel and Conception Vessel were found to be the most commonly selected meridians for asthma treatment in clinical practice.

In using a hierarchical clustering algorithm, 39 acupoints with a frequency greater than 2 were clustered into five major clusters (Fig. 5) signifying the main treatment principles and concepts of "facilitating the flow of the lung Qi, tonifying spleen and kidney, treating both the symptoms and root causes". TCM

distinguishes two general patterns of asthma, an "excess" pattern and a "deficiency" pattern. The former corresponds to an acute asthma attack caused by the obstruction of lung *Qi* due to external pathogenic factor invasion, with symptoms such as chest tightness, severe shortness of breath, wheezing, and fever. The "deficiency" pattern occurs in chronic asthma caused by excessive phlegm resulting from weakened spleen and kidney, the two main *zang* organs responsible for the processing of body liquids. Patients with a "deficiency" pattern complain of wheezing, sweating, and general lassitude with cold hands and feet. In clinic, most patients present with "deficiency-excess complication", of which the impaired functions of the spleen and kidney are root causes. Based on the general principle of "treating both the symptoms and root causes", TCM emphasizes dispelling pathogenic factors and protecting the lungs to treat symptoms, as well as tonifying the spleen and kidney to treat root causes in the treatment of asthma. Thus, acupoint Cluster 1, *Feishu* and *Dingchuan*; Cluster 2, *Lieque* (LU7) and *Yuji* (LU7); and Cluster 3, *Dazhui* and *Fengmen*, were selected to dispel exogenous pathogenic factors, alleviate fever, depress the upward reversal of lung *Qi*, and strengthen the function of the lung to command Qi and control respiration. Acupoint Cluster 4, *Pishu* and *Shenshu*, are used to nourish and tonify the spleen and kidneys, help the kidneys grasp and keep the air (*Qi*) down, and improve the transportation and transformation of body fluid to reduce the production of phlegm. Meanwhile, Cluster 5, including *Danzhong* (CV17), *Tiantu* (CV22), *Gaohuang* (BL43), *Zusanli* (ST36), and *Fenglong* (ST40), were selected to relax the chest, regulate *Qi* and descend the adverse flow of Qi, and dissolve phlegm stagnation in the lungs.

In clinical practice, acupuncturists usually combine more than one acupoint targeting the symptoms and pathogenesis of diseases to enhance the synergy between them and improve the therapeutic effect of acupuncture. In this study, we identified the two most commonly used acupoint combinations in asthma treatment by using an association rule mining techniques (Fig. 6c). One of the most popular acupoint combination was found to be *Pishu*, *Shenshu*, *Feishu*, and *Dingchuan*. *Pishu* and *Shenshu*, two back-shu acupoints that regulate the functions of the spleen and kidney, are used together in asthma treatment because, as mentioned above, TCM believes that the deficiency of the spleen and kidney is an important aetiology of persistent and recurrent asthma attacks. It has been shown that acupuncture at *Pishu* can increase the percentage of CD4^{+} lymphocytes and decrease the percentage of CD8^{+} lymphocytes and, in parallel, increase the production of IL-4 and reduce that of IFN-γ in rats with chronic fatigue [25]. Moxibustion therapy on *Shenshu* and *Zusanli* was found to significantly increase the number of Treg cells and decreased the number of Th17 cells in a mouse model, thereby suppressing collagen-induced arthritis in the mice [26]. These results indicate that acupuncture at *Pishu* and *Shenshu* tends to be effective in regulating immune balance, which is considered to be important for alleviating the airway inflammation caused by asthma. The combination of *Feishu*, *Dingchuan*, and these two acupoints not only can relieve the airway hyperresponsiveness and dyspnea during an asthma attack but can also inhibit the airway inflammatory response stemming from chronic asthma. The other most commonly used acupoint combination was found to be *Feishu*, *Dazhui*, and *Fengmen*, also known as "Three-acupoint and Five-needle therapy" in China. It represents a summary of Professor Shao's clinical experience in treating asthma for years and is used to improve the pulmonary function, strengthen the body's constitution, and prevent the recurrence of asthma. Our previous clinical study indicated that the

total efficacy rate of "Three-acupoint and Five-needle therapy" in the treatment of allergic asthma was 85% [10]. After treatment, the serum levels of total immunoglobin E (IgE) and the IL-2R⁺ T lymphocyte and eosinophil counts in the peripheral blood were significantly decreased. The production of soluble IgA and total IgA in the saliva and nasal secretions of asthma patients was also remarkably decreased [10]. Moreover, proteomic analysis revealed that acupuncture at *Feishu*, *Dazhui*, and *Fengmen* down-regulated the expression of pro-inflammatory proteins (e.g., S100A8, RAGE, and S100A11) and up-regulated the expression of anti-inflammatory proteins (e.g., CC10, ANXA5, and sRAGE) in the lungs of an asthma model [11]. Further experimental studies demonstrated that the combination of these three acupoints reduced $CD4^+ IL-17A^+$ cell numbers and increased $CD4^+ Foxp3^+$ cell numbers in the bronchoalveolar lavage fluid [27], and inhibited the recruitment of pulmonary group 2 innate lymphoid cells (ILC2s) in ovalbumin-induced asthma [28]. Both the theory of TCM and relevant results from modern molecular biological research have provided rationale for the priority use of the acupoint combination of *Pishu*, *Shenshu*, *Feishu*, and *Dingchuan* as well as the combination of *Feishu*, *Dashui*, and *Fengmen* in asthma treatment.

There are several limitations in this study that should be considered. First, the methodological quality of the included studies was relatively low due to the inadequate concealment of the allocations and incomplete outcome data in addition to the fact that fully double-blinding is extremely difficult to achieve for acupuncture treatments. More rigorous randomized controlled trials (RCTs) of acupuncture for asthma will be needed in the future to improve the quality of evidence. Second, the effectiveness of the acupoint prescription in each study was not adequately considered, which was mainly due to unclear control group settings and efficacy evaluation criteria; moreover, this information was not available in some studies. The future well-designed studies with an appropriate control group and efficacy evaluation criteria will enable the extraction of acupoint prescriptions with definite effectiveness. Third, since this current study focuses on the main acupoints in the acupuncture treatment of asthma, data regarding the selection and combination of adjunct acupoints prescribed based on syndrome differentiation was not extracted for analysis. Such data could be further mined in future studies to discover more comprehensive acupoint selection patterns based on TCM syndrome differentiation theory.

Conclusion

In summary, the current study investigated the potential acupoints and combinations for asthma treatment based on a data mining analysis of published CCTs. *Feishu* (BL13), *Dingchuan* (EX-B1), *Dazhui* (GV14), *Shengshu* (BL23), *Pishu* (BL20), and *Fengmen* (BL12) appeared to be the most frequently used acupoints for asthma. The Bladder Meridian of Foot *Taiyang*, the Governor Vessel, and the Conception Vessel, compared to the other meridians, were the more commonly selected meridians. The interconnections between the acupoints were revealed by a network analysis, in which *Feishu* (BL13), *Fengmen* (BL12), *Dingchuan* (EX-B1), and *Dazhui* (GV14) were defined as key node acupoints. The clustering analysis displayed the treatment principle of "facilitating the flow of the lung Qi, tonifying spleen and kidney, treating both the symptoms and root causes". Association rule mining demonstrated

that the combination of *Pishu* (BL20), *Shenshu* (BL23), *Feishu* (BL13), and *Dingchuan* (EX-B1), as well as that of *Feishu* (BL13), *Dazhui* (GV14), and *Fengmen* (BL12) were potential acupoint combinations that should be selected with priority in asthma treatment. Overall, this study provides valuable information for the selection of most effective acupoints and combinations in clinical acupuncture practice and experimental study aimed at the prevention and treatment of asthma.

Abbreviations

ANXA5

Annexin A5; CC10:Clara cell 10 kD protein; CCTs:Controlled clinical trials; CNKI:Chinese National Knowledge Infrastructure; ICS:Inhaled corticosteroids; ILC2s:Group 2 innate lymphoid cells; LABAs:Long-acting beta-2-agonists; LHS:Left-hand side; NIH:National Institutes of Health; RAGE:Receptor for advanced glycation end-products; RHS:Right-hand side; S100A8:S100 calcium-binding protein A8; S100A11:S100 calcium-binding protein A11; SED:Squared Euclidean Distance; sRAGE:Soluble receptor for advanced glycation end-products; TCM:Traditional Chinese Medicine; Th17:T-helper cell 17; Treg:Regulatory T cells; WHO:World Health Organization.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

XYD conceived and designed the study. SPP performed study search, screening, and extraction of data. SPP, CCT, and XYD performed data analysis, whereas YYQ reviewed the work. XYD and SPP wrote the manuscript. CM and SYL revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Niespodziana K, Borochova K, Pazderova P, et al. Toward personalization of asthma treatment according to trigger factors. J Allergy Clin Immunol. 2020;145(6):1529-34.

2. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009;9:24.

3. Korsgaard J, Ledet M. Potential side effects in patients treated with inhaled corticosteroids and long-acting beta2-agonists. Respir Med. 2009;103(4):566-73.

4. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med. 2006;100(8):1307-17.

5. Diver S, Russell RJ, Brightling CE. New and emerging drug treatments for severe asthma. Clin Exp Allergy. 2018;48(3):241-52.

6. Xu YD, Yang YQ, Zheng YJ. G protein-coupled estrogen receptor, a potential therapeutic target of asthma probed by Chinese herb. J Leukoc Biol. 2020;108(1):13-6.

7. Use of acupuncture in modern health care. WHO Chron. 1980;34(7-8):294-301.

8. NIH Consensus Conference. Acupuncture. JAMA. 1998;280(17):1518-24.

9. Choi JY, Jung HJ, Kim JI, et al. A randomized pilot study of acupuncture as an adjunct therapy in adult asthmatic patients. J Asthma. 2010;47(7):774-80.

10. Yang YQ, Chen HP, Wang Y, et al. Considerations for use of acupuncture as supplemental therapy for patients with allergic asthma. Clin Rev Allergy Immunol. 2013;44(3):254-61.

11. Xu YD, Cui JM, Wang Y, et al. Proteomic analysis reveals the deregulation of inflammation-related proteins in acupuncture-treated rats with asthma onset. Evid Based Complement Alternat Med. 2012;2012:850512.

12. Brinkhaus B, Roll S, Jena S, et al. Acupuncture in patients with allergic asthma: a randomized pragmatic trial. J Altern Complement Med. 2017;23(4):268-77.

13. Biernacki W, Peake MD. Acupuncture in treatment of stable asthma. Respir Med. 1998;92(9):1143-5.

14. Jiang C, Jiang L, Qin Q. Conventional treatments plus acupuncture for asthma in adults and adolescent: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019;2019:9580670.

15. Hsieh PC, Cheng CF, Wu CW, et al. Combination of acupoints in treating patients with Chronic Obstructive Pulmonary Disease: an apriori algorithm-based association rule analysis. Evid Based Complement Alternat Med. 2020;2020:8165296.

16. Yu C, Wang L, Kong L, et al. Acupoint combinations used for treatment of Alzheimer's disease: A data mining analysis. J Tradit Chin Med. 2018;38(6):943-52.

17. Lin YH, Wu HC, Hsieh PC, et al. An association rule analysis of combined acupoints for the treatment of patients with dry eye disease. Complement Med Res. 2020:1-8.

18. Borgatti SP. Centrality and network flow. Social Networks. 2005;27(1):55-71.

19. Silverstein C, Brin S, Motwani R. Beyond Market Baskets: Generalizing Association Rules to Dependence Rules. Data Min Knowl Discov. 1998;2(1):39-68.

20. Toti G, Vilalta R, Lindner P, et al. Analysis of correlation between pediatric asthma exacerbation and exposure to pollutant mixtures with association rule mining. Artif Intell Med. 2016;74:44-52.

21. Liu YL, Zhang LD, Ma TM, et al. Feishu acupuncture inhibits acetylcholine synthesis and restores muscarinic acetylcholine receptor M2 expression in the lung when treating allergic asthma. Inflammation. 2018;41(3):741-50.

22. Zhang GS, Qiu RR, Pan J, et al. Effect of moxibustion at Feishu (BL 13) on airway inflammation in asthma model rats. J Acupunct Tuina Sci. 2020;18(3):165-73.

23. SPC N, YMA J. Skin impedance at acupuncture point dingchuan in subjects with and without asthma. Chin J Rehabil Med. 2009;24(6):481-4.

24. Feng JT, Hu CP, Li XZ. Dorsal root ganglion: the target of acupuncture in the treatment of asthma. Adv Ther. 2007;24(3):598-602.

25. Zhang W, Zhang Y, Ma X, et al. Effects of acupuncturing Pishu combined with Ginsenoside Rg3 on the immune function of rats with chronic fatigue. Int J Clin Exp Med. 2015;8(10):19022-9.

26. Zhao C, Li X, Yang Y, et al. An analysis of Treg/Th17 cells imbalance associated microRNA networks regulated by moxibustion therapy on Zusanli (ST36) and Shenshu (BL23) in mice with collagen induced arthritis. Am J Transl Res. 2019;11(7):4029-45.

27. Wei Y, Dong M, Zhang H, et al. Acupuncture attenuated inflammation and inhibited Th17 and Treg activity in experimental asthma. Evid Based Complement Alternat Med. 2015;2015:340126.

28. Cui J, Dong M, Yi L, et al. Acupuncture inhibited airway inflammation and group 2 innate lymphoid cells in the lung in an ovalbumin-induced murine asthma model. Acupunct Med. 2020:964528420924033.
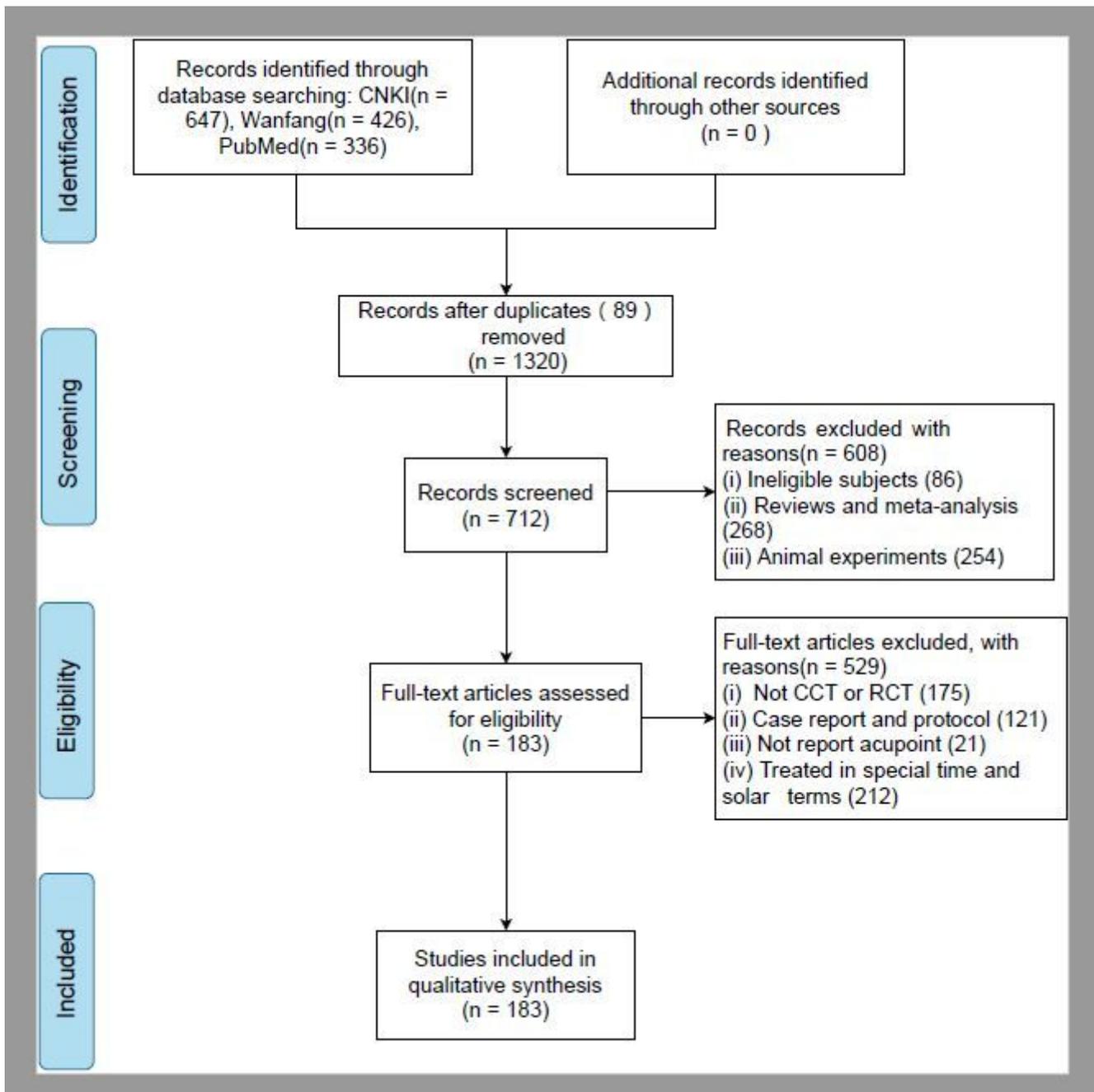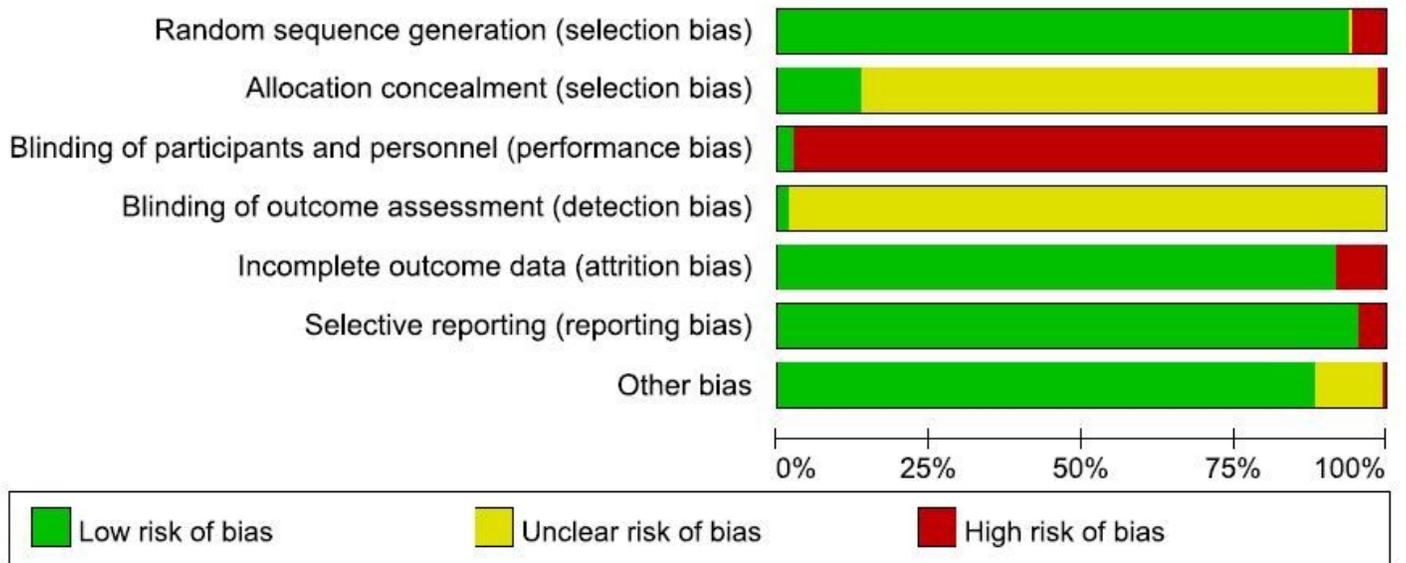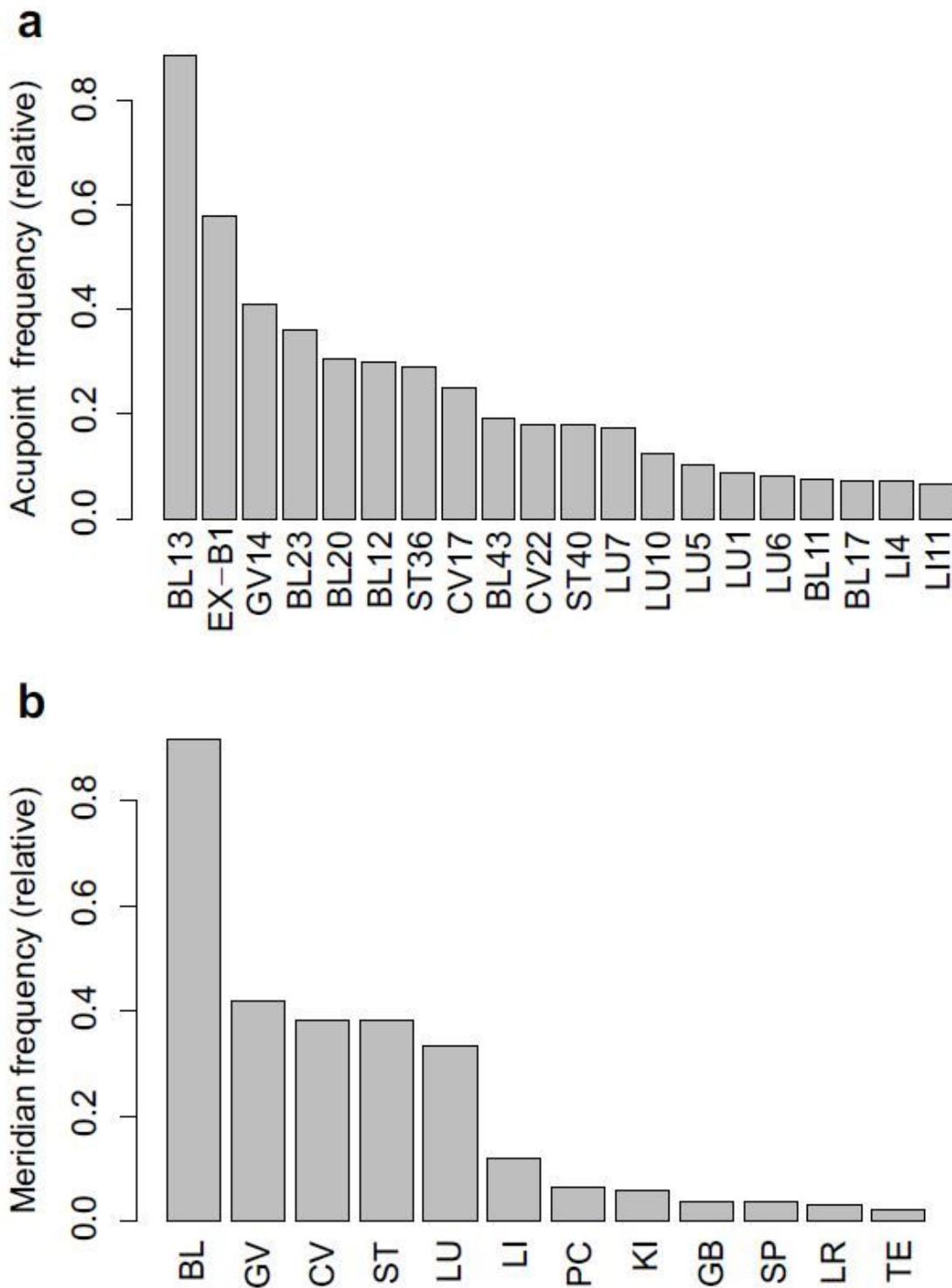
Figures

Figure 1

Flow chart of literature screening process.
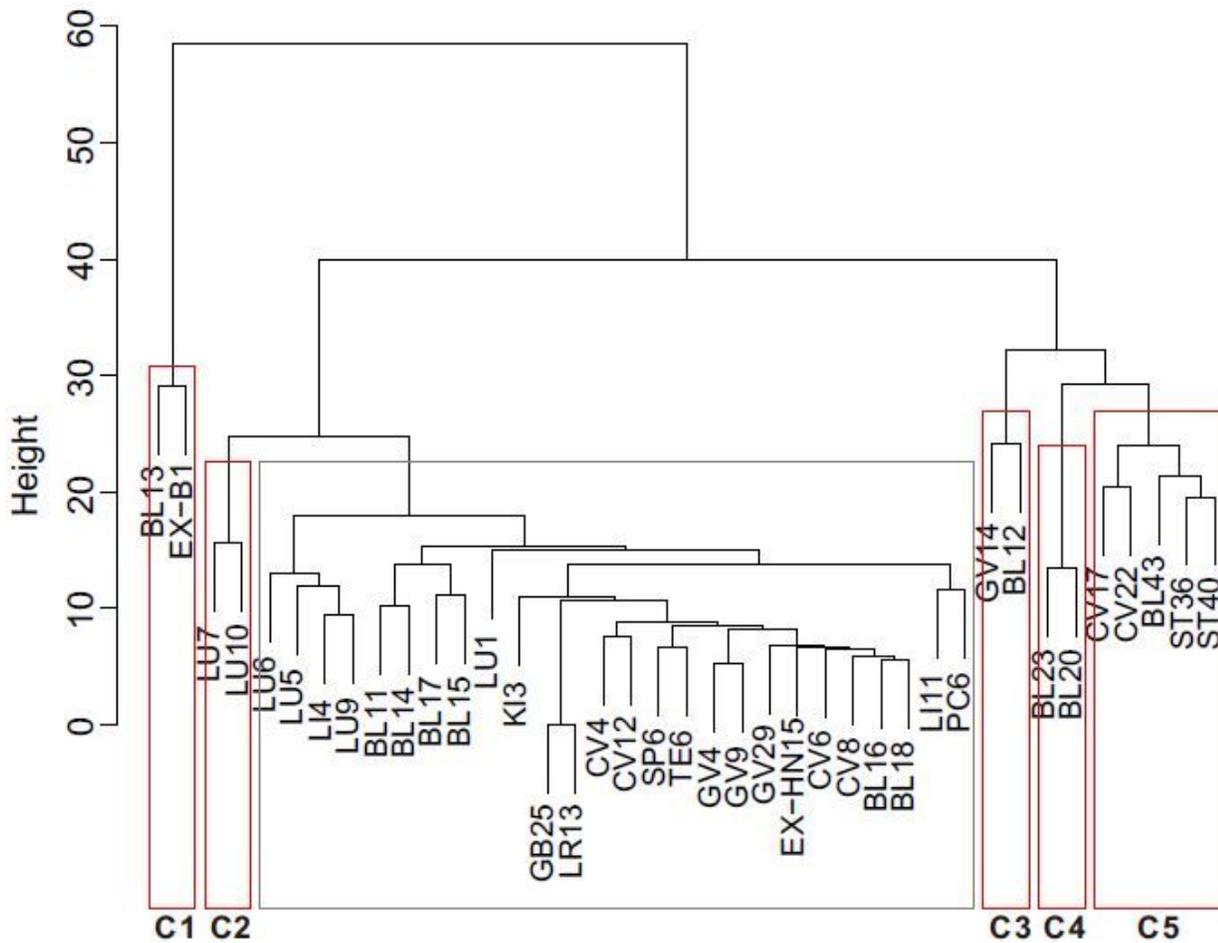
Figure 2

Overall quality assessment of the 183 included controlled clinical trials (CCTs) of acupuncture.
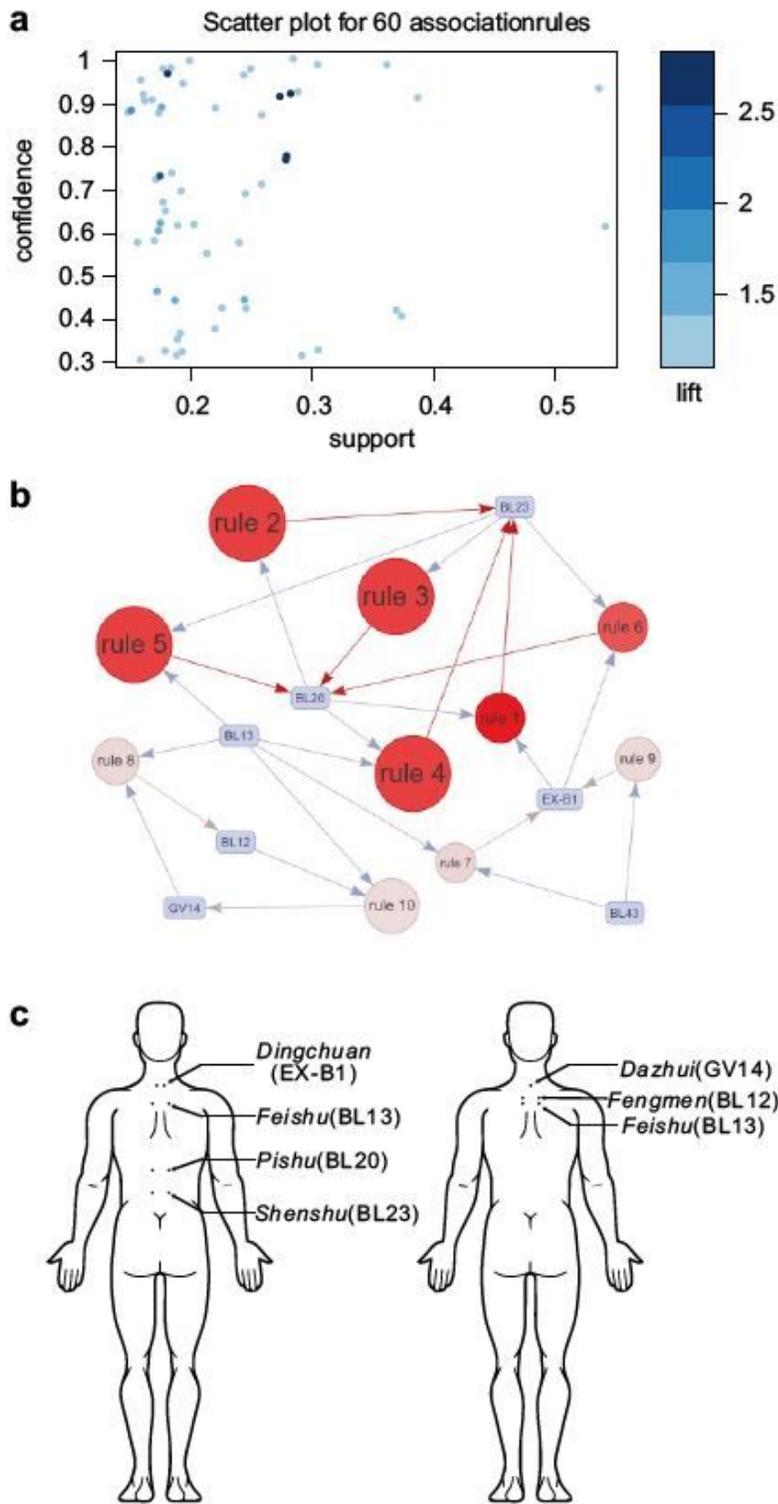
Figure 3

The frequencies acupoints and meridians used in the retrieved CCTs. (a) The top 20 most frequently prescribed acupoints in descending order. (b) The meridian distribution in asthma treatment. BL: Bladder Meridian of Foot Taiyang; GV: Governor Vessel; CV: Conception Vessel; ST: Stomach Meridian of Foot Yangming; LU: Lung Meridian of Hand Taiyin; LI: Large Intestine Meridian of Hand Yangming; PC: Pericardium Meridian of Hand Jueyin; KI: Kidney Meridian of Foot Shaoyin; GB: Gallbladder Meridian of

Foot Shaoyang; SP: Spleen Meridian of Foot Taiyin; LR: Liver Meridian of Foot Jueyin; TE: Triple Energizer of Hand Shaoyang.

Figure 4

Network analysis of acupoints for asthma treatment. The interconnection network between acupoints is visually constructed using Cytoscape software. One node represents a unique acupoint, and the edge is used to represent the cooccurrence of the linked acupoints in a prescription. The degree centrality values of the acupoints are illustrated on a color scale, and the weights of the links between the acupoints correspond to the width of the edges.

Figure 5

Hierarchical clustering dendrogram of acupoints for asthma. The acupoints with a frequency greater than 2 are clustered into four major groups (red box), which are labelled as Cluster 1 (C1), Cluster 2 (C2), Cluster 3 (C3), Cluster 4 (C4), and Cluster 5 (C5), in addition to some minor subgroups (grey box).

Figure 6

Association rule mining of acupoints for asthma. (a) A scatter plot for 60 association rules mined in the retrieved CCTs. The minimum support required was set to 15%, the minimum confidence required was set to 30%, and the maximum number of lift-hand-sides was set to 2. The lift values of these association rules are illustrated on a color scale. (b) Graph-based visualization of the top 10 association rules sorted

by lift value. The rules are shown as circles with color. Color shading is used to indicate the lift value of a rule. (c) Locations of the two best acupoint combinations for treating patients with asthma.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Fig.S1.SpecificacupointAR.pdf
- Fig.S2.MeridianAR.pdf
- SupplementaryFigurelegends.docx
- SupplementaryTables.docx